Diagnostic Utility of Ischemic Modified Albumin in Young Adult Patients with Acute Coronary Syndrome

Genç Erişkin Akut Koroner Sendrom Hastalarında İskemik Modifiye Albumin'in Tanısal Yararlığı

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Özet

Amaç: Bu çalışmayla AKS tanısında IMA'nın yalnız başına ve TnI ile birlikte kullanıldığındaki pozitif ve negatif olabilirlik oranını araştırdık. Çalışma 3 gruba ayrılarak incelendi. Birinci grup normal koroner arterlere sahip vakalardan (n=40), ikinci grup ST segment yükselmesi olan miyokardiyal enfarktüs (STEMI) hastalarından (n=49) ve üçüncü grup ST segment yükselmesi olmayan miyokardiyal enfarktüs - Kararsız Angina (NSTEMI-KA) hastalarından (n=47) oluşturuldu. IMA'nın, AKS hastalarını kontrol grubundan ayırt etmede TnI ve diğer kardiyak markırlardan üstünlüğünün olmadığı görüldü. Ancak AKS hastalarında TnI ve IMA kombinasyonunun, TnI'nin yalnız başına kullanımından daha yüksek bir oranda dışlayıcılığı olduğunu saptadık.

Anahtar Kelimeler

İskemik Modifiye Albumin; Kardiyak Troponin; Akut Koroner Sendrom

Abstract

Aim: In this study, we investigated the diagnostic value of IMA in the positive and negative predictive value of ACS, alone and in combination with TnI. The study population was divided into 3 groups. The first group included those patients with normal coronary arteries (n=40), the second group included the ACS patients with ST segment elevation myocardial infarction (STEMI) (n=49), and the third group included the ACS patients with Non ST-segment elevation myocardial infarction-Unstable Angina (NSTEMI-UA) (n=47). Although its use for diagnostic purposes did not provide an additional benefit for ACS patients, we found that the combination of TnI and IMA could better rule out ACS compared to TnI alone.

Keywords

Ischemia Modified Albumin; Cardiac Troponin; Acute Coronary Syndrome

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality. Early diagnosis and treatment can reduce mortality and mortality [1]. To date, several markers have been identified for the early diagnosis of ACS. Recently, one of these markers, Ischemia Modified Albumin (IMA), has been increasingly used. Formed as a result of the modification of albumin due to the reactive oxygen species (ROS) that is released due to muscular damage of the hypoxic cardiac tissue, IMA was first discovered in the 1990s [2]. The FDA (Food and Drug Administration of the USA) approved the IMA test in 2003 to rule out acute myocardial infarction in patients who present to the emergency department with chest pain [3]. The IMA level in the blood starts elevating within 10 minutes following ischemia and continues elevating as ischemia persists [4]. This time is much shorter than the time required for other cardiac markers to appear in the blood.

The markers for ischemia are useful to assess ischemia at an earlier stage, to prevent its progression into infarction, and to avoid further complications. The aim of this study was to investigate the diagnostic value for ACS of the other cardiac markers and of IMA alone and in combination with TnI in ACS patients younger than 50 years of age who present to emergency departments with acute cardiac ischemia symptoms.

Material and Method

Study Group

136 patients aged 21 to 50 were included in the study. All patients were selected from among those who underwent angiography. According to the results of clinical examination, ECG, test for cardiac markers, and angiography, the study population was divided into three groups: group 1 (n=40), group 2 (n=49), and group 3 (n=47). Group 1 included patients who did not have significant stenosis (coronary stenosis lower than 50%) according to the angiography results; group 2 included ACS patients who were considered to have STEMI; group 3 included ACS patients considered to have NSTEMI-UA. Troponin I, CK-MB, and myoglobin were analyzed by the chemiluminescence method on the Siemens ADVIA Centaur CP (Siemens Healthcare, Erlangen, Germany) device.

Study Design

This prospective study was conducted at the Central Biochemical Laboratory of Antalya Training and Research Hospital from May 2013 to January 2015. It was conducted in collaboration with the Emergency Department, where an average of 185,000 patients present annually due to non-traumatic reasons, and with the Cardiology Department, where an average of 5,000 percutaneous coronary procedures (of which an of average 1,500 are urgent) are performed annually. Patients who had other cardiac problems such as acute pericarditis and cardiac failure, diseases such as liver failure that affect the albumin level, renal failure, malignancies, and cerebrovascular diseases were excluded from the study. ECG with 12 derivations was performed for all patients who presented to the emergency department within 3 hours following the onset of the symptoms and who conformed to the inclusion criteria at admission. Their troponin I (TnI), myoglobin, creatinine kinase MB (CK-MB), and

IMA and albumin levels were analyzed.

Biochemical Analysis

IMA was measured by the albumin cobalt-binding test that was defined by Bar-Or et al. (2). This test is based on the colorimetric measurement of the colorful complex formed by cobalt that is attached to the sample and does not bind to albumin with dithiothreitol (DDT). For the measurement, cobalt chloride solution of 0.1%, 1.5 mg/ml DTT solution, 0.9% NaCl solution, glass tube, vortex, adjustable automatic ependorff pipette, disposable plastic micro cuvette, and Shimadzu UV-120V model spectrophotometer were used. CoCl26H2O (Sigma-Aldrich Lot: S38901-248), DTT solution, and DTT (Sigma-Aldrich Lot: D5545-1G) chemicals were dissolved in the distilled water to prepare the cobalt chloride solution. After 50 µl 0.1% cobalt chloride solution was added to each patient's blood serum of 200 µl, the mixture was vortexed and incubated for 10 minutes for albumin-cobalt binding. In order to create the color reaction for the cobalt that was not bound by the albumin by the end of incubation, 50 µl 1.5 mg/ml DTT solution was added to the mixture and kept for 2 minutes. After 2 minutes, 1 ml 0.9% NaCl was added to the mixture to complete the reaction. The same steps were taken simultaneously for the samples that were prepared, using distilled water instead of DTT. By the end of the reactions, the differences between the absorbance values of the samples and sample blinds read at 470 nm were recorded as İMA values. The results were recorded as absorbance units (ABSU). All procedures were performed simultaneously by two practitioners. All reactions were realized in glass tubes. All measurements were completed within 3 days. Intra-assay CV (coefficient of variation) and inter-assay CV were found to be lower than 3% in the precision assay performed with the serum pool.

Statistical Analysis

The data obtained from this study were recorded in the SPSS 21.0 (Armonk, NY: IBM Corp.) software. Data were expressed as numbers and percentage for categorical variables and as mean ± standard deviation for continuous variables. Shapiro Wilk test was performed to analyze the concordance of the continuous variables with the normal distribution. The significance of the difference between the ACS patients and the control group with respect to the IMA, TnI, myoglobin, and CK-MB levels was analyzed with Kruskal Wallis test. The significance of the sub-group comparisons was calculated through the Bonferroni correction. In bilateral comparisons between the groups, Student-t test was used for the normally distributed parameters while Mann-Whitney U test was used for the parameters that were not normally distributed. Chi-Square test or Fisher test was used for the analysis of the categorical variables. The effectiveness of the IMA measurement to distinguish the ACS patients from the control group was analyzed by calculating the sensitivity and specificity of the area below the ROC curve. $P < 0.05$ was considered as statistically significant.

Results

14.0% (n=19) of 136 patients included in the study were female while 86.0% (n=117) were male. The mean age of the patients was 43.3±6.3. The comparison between the patients with re-

gard to age, sex, and the traditional risk factors for CAD—hypertension (HT), diabetes mellitus (DM), hyperlipidemia, family history, and smoking—revealed a significant difference between the patient groups in sex, smoking, and hyperlipidemia (Table 1).

The significant differences between the patient groups in the mean values of TnI, CK-MB, myoglobin, and IMA are presented in Table 2. The IMA levels of the patients in groups 2 and 3 who were considered to have ACS were significantly higher than those in group 1 (0.454±0.08, 0.414±0.08 vs 0.404±0.04, p=0.006; Figure 1). The bilateral sub-group comparisons between the groups with respect to IMA levels revealed a significant difference between group 1 (control) and group 2 (STEMI), and between group 1 (control) and group 3 (NSTEMI-UA), whereas there was no significant difference between group 2 (STEMI) and group 3 (NSTEMI-UA) in that regard (0.404±0.04 vs 0.454±0.08, p=0.002; 0.404±0.04 vs 0.414±0.08, p=0.015; 0.454±0.08 vs 0.414±0.08, p=0.416, respectively).
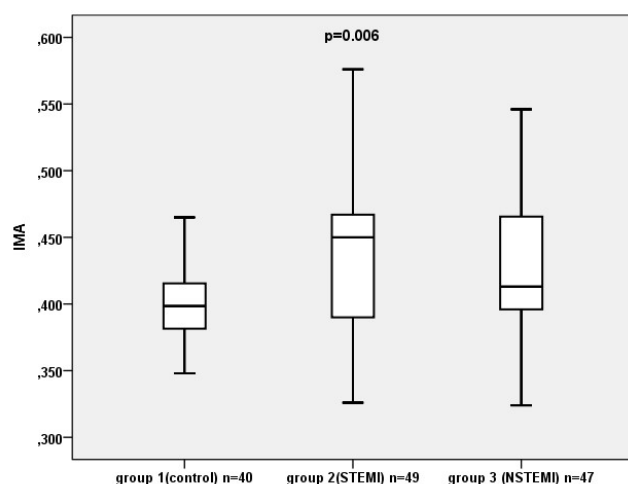
When the cut-off value of IMA level was considered as 0.443 ABSU on the ROC curve to distinguish the acute STEMI patients from the control group, the sensitivity and specificity were found to be 61.2% and 87.5%, respectively, while the negative predictive value was 64.8% and the positive predictive value was 85.7% (AUC:0.692, 95% CI: 0.580-0.804) (Figure 2).

When the cut-off value of IMA level was considered as 0.455 ABSU on the ROC curve to distinguish the patients in Group 3 (NSTEMI-UA) from those in group 1 who were the control patients, the sensitivity and specificity were found to be 36.2% and 90.0%, respectively, while the negative predictive value was 54.5%, and the positive predictive value was 81.0% (AUC:0.644, 95% CI: 0.528-0.761).

When the reference range for TnI was considered as 0.01-0.06 ng/ml, 38.8% (n=19) of the patients in Group 2 and 25.5% (n=12) of the patients in Group 3 had a normal TnI range at admission. TnI that was used to distinguish the acute STEMI patients from the control group was found to have a sensitivity of 61.2%, specificity of 95.0%, negative predictive value of 66.7%, and positive predictive value of 93.8% (p<0.001). When used in combination with IMA (when the reference range was 0.0-0.443), the sensitivity and specificity of TnI for acute STEMI were found to be 63.2% and 97.1%, respectively, while the negative predictive value was 82.9% and positive predictive value was 92.3% (Table 3; Figure 3).

The sensitivity, specificity, negative predictive value, and positive predictive value of TnI when used to distinguish the NSTEMI-UA patients from the control group were found to be 76.6%, 95.0%, 77.6%, and 94.7%, respectively (p<0.001). The sensitivity, specificity, negative predictive value, and positive predictive
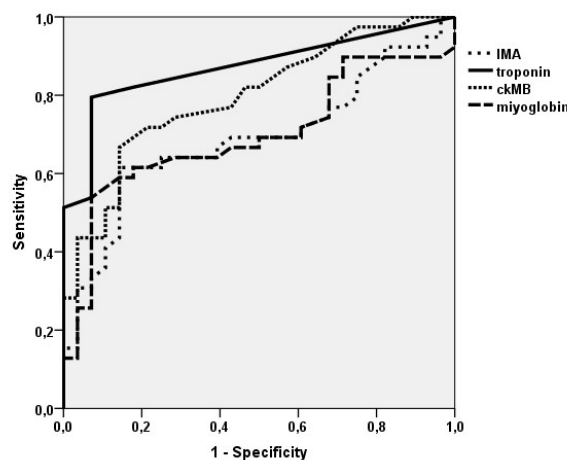
Table 1. Demographic characteristics of the study groups.

	Group I (healty control) (n=40)	Group II (STEMI) (n=49)	Group III (NSTEMI-UA) (n=47)	p value
Male, n(%)	28 (%70.0)	45 (%91.8)	44 (%93.6)	0.002
Age, years	41.40±6.2	43.80±6.9	44.36±5.6	0.104
DM, n(%)	2 (%5.0)	6 (%12.2)	5 (%10.6)	0.597
HL, n(%)	4 (% 10.0)	14 (% 28.5)	16 (% 34.0)	0.037
HT, n(%)	3 (%7.5)	11 (%22.4)	9 (%23.4)	0.366
Smoking, n(%)	17 (%42.5)	38 (%77.5)	22 (%46.8)	0.019
Family History, n(%)	20 (% 50.0)	22 (%48.8)	28 (% 59.5)	0.430

(Data are expressed as mean ± standard deviation for normally distributed data and percentage for categorical variables.) (DM: Diabetes Mellitus, HL:Hyperlipidemia)

Table 2. Biochemical values of study groups.

	Group I (healty control) (n=40)	Group II (STEMI) (n=49)	Group III (NSTEMI-UA) (n=47)	p value
IMA, ABSU	0.404±0.04	0.454±0.08	0.414±0.08	0.006
TnI, ng/ml	0.007±0.01	6.581±16.0	1.293±3.4	<0.001
Myoglobin, ng/mL	43.5±56.8	151.2±241.1	94.8±131.9	0.002
CK-MB, ng/mL	1.13±72.4	28.1±72.4	9.9±19.8	<0.001

(which show a normal distribution mean ± SD)

Figure 1.

Figure 2.

Table 3. Clinical characteristics of TnI, IMA and their combination for detection of STEMI

	TnI	IMA	TnI (Patients with IMA≤0.443)	IMA (Patients with normal TnI)
p value	<0.000	0.002	<0.000	<0.000
Sensitivity	61.2%	61.2%	63.2%	75.0
Specificity	95.0%	87.5%	97.1%	82.9
NPD	66.7%	64.8%	82.9%	89.5
PPD	93.8%	85.7%	92.3%	63.2

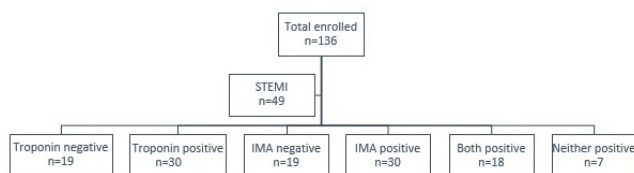(NPD: negative predictive value, PPD:Positive predictive value)

Figure 2.

value of TnI when used in combination with IMA (when reference range was 0.0-0.455) to distinguish NSTEMI-UA were found to be 80.0%, 94.4%, 85.0%, and 92.3%, respectively.

Discussion

Biomarkers play a pivotal role in the diagnosis and management of patients with ACS [5]. However, several markers used for the diagnosis of ACS do not provide the desired level of diagnostic support in the presence of myocardial ischemia without necrosis. Even Troponin, which is the most widely used and most reliable marker, can only be detected in the blood 3-6 hours following myocardial necrosis [6].

IMA, which is one of the markers that have been studied to detect early ischemia, is also recommended in the ACS guidelines [7]. Measurement of the serum IMA level seems to be more advantageous in the diagnosis of cardiac ischemia compared to the other biochemical markers. IMA yields a positive result within a few minutes to a few hours following ischemia before myocardial necrosis develops [8].

Studies of the use of IMA for the diagnosis of ACS report conflicting results. Some researchers have argued that IMA was helpful to diagnose ACS when used alone, while some others claim it had no benefit.

In the study conducted by Roy et al. in which they investigated the patients who presented with chest pain but had normal or non-diagnostic ECG findings and negative TnT values, they found that IMA values were significantly higher in patients with myocardial ischemia compared to those who did not have myocardial ischemia. When used alone to detect myocardial ischemia, IMA's sensitivity was found to be 75.0%, whereas it rose up to 82.8% when used in combination with TnT [9]. In another study comprising 675 cases, it was found that IMA could be especially helpful in detecting early ACS patients for whom TnI failed [10].

Reddy et al. investigated 3 groups of patients (non ischemic chest pain (NICP), unstable angına (UA), and myocardial infarction (MI)) and reported a similar finding, stating that IMA had a high sensitivity (92.0%) and specificity (88.0%) in detecting ischemia. In that study, they also concluded that IMA could be used as a rule-out criterion due to its high negative predictive value (94.0%) to detect early ACS [11].

Contrary to the results of the abovementioned studies, Çevik et al. evaluated the diagnostic performance of copeptin, TnI, and IMA to detect STEMI patients in a series of 26 cases and concluded that IMA did not have an additional diagnostic value when used either alone or in combination with TnI [12]. Soren et al. evaluated 107 cases and similarly reported that IMA was not superior to the other biomarkers and it would not be useful in diagnosing ACS in ERs [13]. Given that the guidelines specify that treatment should be started for patients diagnosed with

STEMI through ECG without waiting for the TnI results, these findings are not surprising. Similar to the abovementioned studies, we also observed that IMA values did not provide any additional diagnostic value for the patients diagnosed with STEMI. Several studies have reported that IMA can be used as a marker to rule out ACS due to its high negative predictive value [14,15]. Takhshid et al. reported that IMA had a negative predictive value of 88% to rule out ACS when used alone, while it was 96.0% when used in combination with TnI and ECG [16]. Lee et al. also reported a high negative predictive value for IMA. In that study, the sensitivity of IMA was found to increase markedly when combined with TnI and CK-MB as the other cardiac markers [17]. In a meta-analysis performed on 1,800 patients, the combination of IMA, ECG, and troponin was found to rule out myocardial ischemia by 97.1% [18].

Limitations

Our study was conducted in a single center, which may limit the generalizability of our results. The majority of the studies investigating IMA levels have used U/ml as the unit of measure. We used ABSU in our study; therefore, we could not make a comparison with the cut-off values of the other studies. Furthermore, we used a standard troponin I test because our institution did not have a high-sensitivity troponin I test.

Conclusion

Although troponin is considered a gold standard for the diagnosis of ACS, the troponin values of a significant number of ACS patients at admission were below the level required to take a clinical decision. IMA, which was supposed to be an alternative to troponin and other cardiac markers, was not observed to have the expected benefit for the diagnosis of ACS in our study. Contrary to the studies proposing that IMA could be used to rule out ACS, we found that it could only have a significant negative predictive value when used in combination with TnI for ACS patients.

Competing interests

The authors declare that they have no competing interests.

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